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REVIEW ARTICLE

'African Potato' (*Hypoxis hemerocallidea* corm): A Plant-Medicine for Modern and 21st Century Diseases of Mankind? – A Review

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The traditional uses, therapeutic attributes, phytochemical and pharmacological profiles of 'African potato' (*Hypoxis hemerocallidea* corm) extracts have been reviewed. Available biomedical evidence suggests that 'African potato' is a potential plant-medicine for some modern and 21st century diseases of mankind. Thus far, biomedical evidence has revealed that 'African potato' extracts possess antiinflammatory, antineoplastic, antioxidant, antidiabetic and antiinfective properties *in vivo* and *in vitro*. However, more laboratory and clinical studies are required to clarify these observations, and to isolate, purify and characterize the active chemical constituents responsible for the herb's pharmaco-therapeutic effects. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: traditional herbal medicines; 'African potato' extracts; plant-medicine; pharmaco-chemical profiles; therapeutic attributes.

INTRODUCTION

African Traditional Medicines and 'African Potato'

It has been estimated that about 80% of the general population in sub-Saharan Africa use African traditional medicines (Hostetmann *et al.*, 2000; Puckree *et al.*, 2002) and that as many as 100 000 traditional healers are in practice in South Africa alone, with a contingent of herbal trade industry worth approximately R500 million per annum (Mander, 1998). It has also been estimated that the ratio of traditional healers and orthodox medical doctors to the population in South Africa is 1:500 and 1:40 000, respectively (Abdool-Karim *et al.*, 1994). Traditional medicine, therefore, plays a critical role in the healthcare delivery system of South Africa, given the poor state of healthcare infrastructure, increased disease burden occasioned by the HIV/AIDS pandemic, and other chronic ailments that Western medicines have failed to cure. The importance of herbal medicines (phytomedicines) in this regard is only now being appropriately recognized. The Ministries of Health of several African countries have recently formulated policies that promote the use of African traditional medicines for the management, control and treatment of HIV/AIDS-related diseases and other chronic ailments of man (Morris, 2002; Southern Africa Development Community, 2002).

The recent renewed interest in African traditional medicines has attracted the attention of not only government and private research laboratories and institutes, but also of pharmaceutical industries, in order to rationalize the scientific and therapeutic values of African traditional medicines. One African medicinal plant that has enjoyed long usage as a traditional herbal medicine in southern Africa is *Hypoxis hemerocallidea* (also known as *H. rooperi*). This popular 'miracle' medicinal plant is widely distributed in the southern Africa sub-region. The plant is characterized by strap-like leaves, and bright yellow, star-shaped flowers (Van Wyk *et al.*, 2002). The tuberous rootstock (i.e. the corm) of the plant is commonly referred to as 'African potato', because of its potato-like shape. Traditionally, after washing with clean water, the plant's corms are chopped into small pieces, boiled for about 20 min, and then the decoction is consumed orally. This oral administration is estimated to correspond to a daily dose of 250 mL, derived from about 20 g of the corms (Nair *et al.*, 2007a; Pujol, 1990). 'African potato' extracts, powders, infusions and decoctions have been used for centuries by southern African traditional healers for the treatment, management and/or control of an array of human ailments, including cancers, nervous disorders, immune-related illnesses, heart weaknesses and urinary tract infections (Singh, 1999). Indeed, among the Swazis of Swaziland, *Hypoxis hemerocallidea* is often referred to in siSwati as '*zifozonke*', meaning: 'the plant that can be used to treat many diseases' (Amusan *et al.*, 2007). Some of the outstanding critical questions that still require answers about 'African potato' include: (i) what has made 'African potato' so unique in the family of 'African herbal medicines', and (ii) why has it taken researchers and healthcare providers so long a time to exploit and maximize the potential therapeutic benefits of this 'wonder' plant-medicine?

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BIOLOGICAL ACTIVITY

Therapeutic and pharmacological considerations

In recent years, attempts have been made to investigate the scientific basis of the therapeutic claims attributed to 'African potato'. Evidence-based laboratory investigations indicate that aqueous and alcohol extracts of 'African potato' possess many interesting pharmacological properties, including antinociceptive (in mice), antiinflammatory and antidiabetic properties (in rats) *in vivo* (Ojewole, 2006). 'Intraperitoneal injections of 50–800 mg/kg body weight of "African potato" extracts produced significant and dose-dependent anti-nociceptive effects against chemically- and thermally-induced nociceptive pain in mice' (Ojewole, 2006). At the same dose level, oral administrations of *H. hemerocallidea* corm extracts also 'significantly inhibited egg albumin-induced acute inflammation, and reduced blood glucose levels in both normal and streptozotocin-induced diabetic rats in a dose-dependent manner' (Ojewole, 2006). These observations, therefore, suggest that extracts of 'African potato' could possess antiinflammatory and antidiabetic (hypoglycaemic) properties, respectively. As suggested by Ojewole (2006), the extracts of 'African potato' could inhibit the synthesis, production and/or release of inflammatory cytokines and mediators such as prostaglandins. Recent reports have indicated that lectin-like proteins purified from aqueous extracts of 'African potato' can inhibit cyclooxygenase (COX) enzyme that mediates prostaglandin synthesis *in vitro* (Gaidamashivili and Van Staden, 2006). However, other studies have shown that ethanol extracts of *H. hemerocallidea* have higher inhibitory effects on COX-1 catalysed prostaglandin synthesis than aqueous extracts of the plant's corms (Steenkamp *et al.*, 2006). Aqueous extracts of *H. hemerocallidea* corms have previously been shown to scavenge free radicals (hydroxyl ions) *in vitro* (Mahomed and Ojewole, 2003), and it has been suggested that the ability of the corm's extracts (both aqueous and ethanol) to suppress inflammation could be mediated via its antioxidant activity which, in turn, inhibits COX enzymes (Feng *et al.*, 1995; Kumagai *et al.*, 2000; Mahomed and Ojewole, 2003; Steenkamp *et al.*, 2006). Taken together, these observations appear to suggest that the reported antiinflammatory activity of 'African potato' extracts could be due to their ability to inhibit the synthesis of prostaglandins and other inflammatory mediators (see Fig. 1).

It has been reported that lectin-like proteins derived from extracts of 'African potato' inhibited the growth of *Staphylococcus aureus*, *in vitro* (Gaidamashivili and Van Staden, 2002). Undoubtedly, agglutinins, found in the storage parts (corms) of *H. hemerocallidea*, play a critical role in the plant's defensive mechanism against pathogenic micro-organisms. This observation would, therefore, support the age-old usage of 'African potato' in the treatment of microbial infective disorders (Hutchings *et al.*, 1996; Van Wyk *et al.*, 2002). Laboratory reports have further shown that both ethanol and aqueous extracts of *H. hemerocallidea* corm inhibit the growth of *Escherichia coli, in vitro* (Steenkamp *et al.*, 2006), an observation quite consistent with the previously

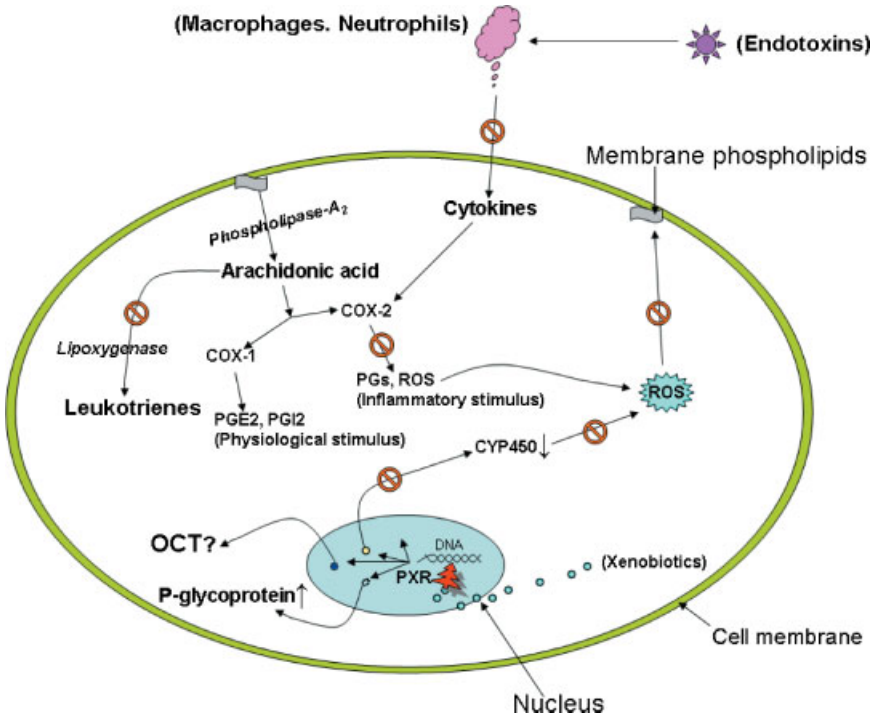

Figure 1. A summary of the putative pharmacological actions of 'African potato' extracts (rooperol and stigmasterol) on some cellular pathways so far investigated. Antiinflammatory activity of 'African potato' extracts could be attributed to inhibition of lipoxygenase, cyclooxygenase (COX) and cytokines production. Antioxidant activity of the extracts could be mediated via reduced reactive oxygen species (ROS) production, either from diminished activity or expression of drug metabolizing enzymes, or from direct inhibition of COX. Increased expression of pregnane X receptor (PXR) binds xenobiotics and triggers over-expression of P-glycoproteins and some drug metabolizing enzymes, thus causing toxicity related to drug resistance or herbal drug reactions. Effects of 'African potato' extracts on organic cation transporters (OCT) are not known. ⊘ = inhibitory effects of 'African potato' extracts; ⊙ = xenobiotics; ↑ = up-regulation/stimulation; ↓ = down-regulation/inhibition.

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reported antibacterial activity of 'African potato' (Gaidamashivili and Van Staden, 2002). *Escherichia coli* infection is the most common secondary cause of bacterial prostatitis (Steenkamp *et al.*, 2006). This observation may, therefore, partly also explain the traditional usage of the extracts of this plant's corm in the treatment of urinary tract infections (Singh, 1999).

Benign prostate hyperplasia (BPH) can cause blockade of the urinary tract in men, and this may lead to chronic bacterial prostatitis. Anecdotal and folkloric reports have documented that 'African potato' extracts have been used traditionally in the treatment of prostate hyperplasia (Singh, 1999). The observation that 'African potato' extracts can inhibit the growth of *E. coli in vitro*, therefore, seems to support the use of this plant's corm in the treatment of prostate hyperplasia. Furthermore, therapeutically useful steroids are present in *Prunus africanum* and *H. hemerocallidea*. However, more recent experimental and clinical evidence have suggested that the effects of *H. hemerocallidea* corm extracts on BPH might not only be due to their antibacterial activities, but could also be due to their antiinflammatory and antioxidant properties (Ojewole, 2002; Steenkamp *et al.*, 2006; Nair *et al.*, 2007b). This body of evidence, therefore, supports the claims that 'African potato' extracts may contain chemical compounds that suppress tumour growth, and hence, its use in the treatment of cancers.

It has recently been shown that aqueous extracts of 'African potato' caused bradycardia and brief hypotension in guinea-pigs and rats *in vitro* and *in vivo*, respectively (Ojewole *et al.*, 2006). Although the investigators were unable to establish the precise pharmacological mechanisms underlying their observations, they ruled out involvement of the cholinergic system, since the cardio-depressant effects of the extracts were not modified by atropine pretreatment (Ojewole *et al.*, 2006). However, in an earlier study using Chacma baboons, Coetzee *et al.* (1996) reported that a purified extract of *H. hemerocallidea* corm (rooperol) increased myocardial contractility *in vivo*. Recently, a case study was published where it was reported that chronic ingestion of aqueous extract of 'African potato' (as tea) caused ventricular tachycardia in a 25-year-old male subject (Ker, 2005). The above conflicting cardiovascular observations tend to suggest that extracts of *H. hemerocallidea* corm contain some bioactive chemical compounds with cardiovascular activities. These findings may also lend pharmacological credence to the age-old usage of this plant in the treatment and/or management of heart ailments and hypertension in some rural communities of southern African.

However, what has recently stimulated the greatest interest, not only among traditional healers and their patients, but also in scientific communities, the pharmaceutical industries, as well as in government circles, is the claim that *H. hemerocallidea* corm can boost human immune system. Some healthcare providers in South Africa are currently using extracts of *H. hemerocallidea* corms as immunostimulant preparations for patients living with HIV/AIDS, on the strength of the recommendation of South Africa's national Department of Health (Southern Africa Development Community, 2002; Mills *et al.*, 2005a). In this regard, the use of this plant's corms has been extended to immune-related illnesses, such as common cold, flu and arthritis (Mills *et al.*, 2005a). Unfortunately, despite the popular belief in the immune-boosting properties of this plant's corms, there is absolutely no laboratory or clinical evidence yet to support this immunostimulant claim, which at present still remains speculative. Many clinical and laboratory studies are, however, currently under way to substantiate or refute the immunostimulant property attributed to 'African potato' extracts.

PHYTOCHEMISTRY

Chemical constituents

Hypoxis hemerocallidea corm has a catalogue of anecdotal, folkloric and therapeutic uses. Undoubtedly, 'African potato' is one of the most popular and ethnobotanically acknowledged medicinal plants in southern Africa (Drewes and Khan, 2004). Attempts have been made in some laboratories to isolate, purify and characterize the chemical constituents of this plant's corm that could be responsible for its medicinal properties. One of the most important chemical constituents of the herb which has been confirmed to be abundantly present in extracts of 'African potato' is a norlignan diglucoside, hypoxoside, a biologically inactive pro-drug (Marini-Bettolo *et al.*, 1982), with an uncommon aglycone structure, consisting of diphenyl-1-en-4-yne-pentane skeleton (Nair and Kanfer, 2006a; Nair *et al.*, 2007a). Hypoxoside is reported to have low toxicity, hence, the traditional consumption of 'African potato' as a food (Drewes *et al.*, 1984; Smit *et al.*, 1995). In the human gut, hypoxoside is converted to rooperol, a biologically active compound, by beta-glucosidase enzyme, which is abundantly present in the human gut and rapidly dividing cancer cells (Mills *et al.* 2005a) – see Fig. 2.

Both rooperol and its pro-drug, hypoxoside, have been shown to undergo phase I hepatic metabolism by cytochrome P_{450} (probably CYP 3A4) enzyme, while their phase II metabolic products, consisting of diglucuronide, disulphate and mixed glucuronide-sulphates, are eliminated by first-order kinetics (Albrecht *et al.*, 1995a; Mills *et al.*, 2005b). Rooperol can be recovered from these metabolites by deconjugation reactions (Albrecht *et al.*, 1995b). Most of the therapeutic properties of 'African potato' extracts observed clinically in man and in laboratory animals to date, have been attributed to rooperol (Albrecht *et al.*, 1995a; Albrecht *et al.*, 1995b; Vinesi *et al.*, 1990). Rooperol has been shown to be antineoplastic, bacteriostatic and bactericidal (Drewes *et al.*, 1984; Drewes and Khan, 2004; Albrecht *et al.*, 1995a). It has been suggested that the antimetastatic activity of rooperol could be mediated through its ability to stimulate the synthesis of collagen type I that could impede cell invasions (Dietzsch *et al.*, 1999). However, hypoxoside as an oral pro-drug, has failed to exhibit any toxicity in phase I clinical trials for cancer therapy (Smit *et al.*, 1995; Albrecht *et al.*, 1995a; Albrecht *et al.*, 1995b). Recent laboratory investigations have shown that rooperol has a strong antioxidant activity, a strong affinity for phospholipid membranes, and that it inhibits free radical-induced membrane lipo-oxidation (Laporta *et al.*, 2007) – see Fig. 1. These findings seem to suggest that rooperol is important in the maintenance of cell membrane stability (Hostetmann *et al.*, 2000), a phenomenon

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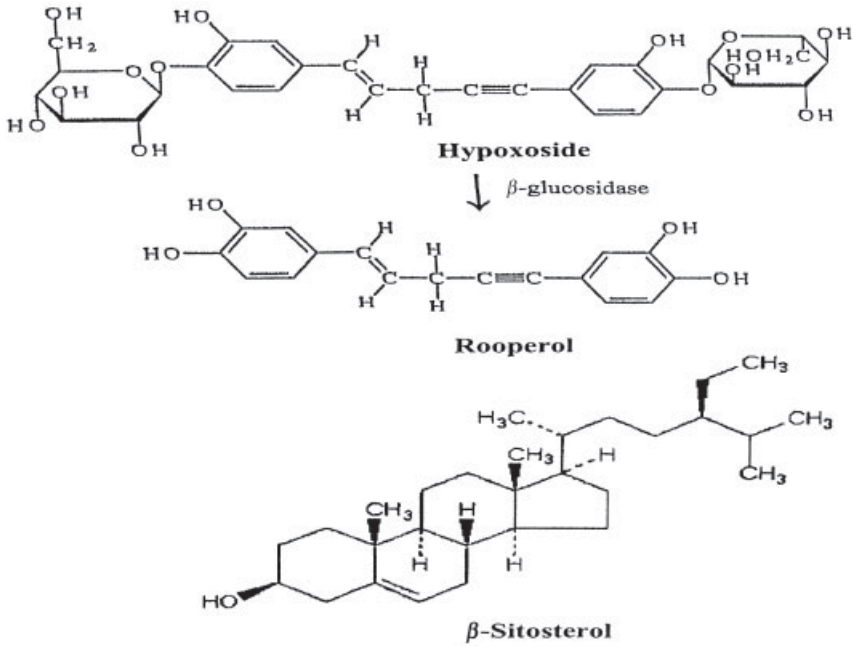

Figure 2. Structures of hypoxoside, rooperol and β-sitosterol. The biologically inactive norlignan diglucoside, hypoxoside, is deconjugated and converted by β-glucosidase enzyme to form the biologically active aglucone, rooperol.

which may partially explain its activity against neoplastic cells.

It is still unclear at the moment, whether the ability of rooperol to inhibit inflammatory processes *in vitro* and *in vivo*, is as a consequence of its direct ability to inhibit the production of pro-inflammatory cytokines, tumour necrosis factor (TNF)-α, and interleukins; or due to its inhibitory effects on enzymes involved in the synthesis of pro-inflammatory mediators, such as leukotrienes and prostaglandins. In an earlier study, Van der Merwe *et al.* (1993) showed that rooperol is a potent inhibitor of lipo-oxygenase (an enzyme that catalyses the first-step in the conversion of arachidonic acid to leukotrienes), but not cyclooxygenase (COX), which catalyses the rate-limiting step in the conversion of arachidonic acid to prostaglandins (Fig. 1). Subsequent study by Guzek *et al.* (1996), in an investigation which attempted to highlight the potential therapeutic benefit of 'African potato' extracts in the treatment of airways inflammatory diseases, showed that rooperol and its derivatives inhibit the production of TNF-α, interleukin1-β and interleukin-6, and also suppress the production of nitric oxide *in vitro*. However, direct inhibitions of COX-1 (constitutive) and COX-2 (inducible) isoforms of the COX enzymes by extracts of *H. hemerocallidea* corm, have also recently been reported (Gaidamashivili and Van Staden, 2006; Steenkamp *et al.*, 2006). Despite the prevailing uncertainties about the precise mechanism/s by which rooperol exerts its antiinflammatory effects, it is important to recognize that rooperol shares intimate structural similarity with a well-known, strong antioxidant, nordihydroguairectic acid (Nair *et al.*, 2007b), and comparably inhibits leukotriene and prostaglandins synthesis in polymorphonuclear leukocyte and platelet microsomes, respectively (Van der Merwe *et al.*, 1993; Coetzee *et al.*, 1996). On the strength of the available scientific, pharmacological and clinical evidence, several patents have been registered on rooperol, and the extract has also been registered under the trade name of 'Harzol™' in Germany for the treatment of prostate cancer (Pegel, 1979; Tyler, 1986; Drewes and Lieberg, 1987; Albrecht *et al.*, 1995a; Nair *et al.*, 2007a). At present, there are numerous commercial herbal preparations which contain rooperol or extracts of 'African potato' in the market for the treatment, management and/or control of many modern and 21st century diseases of man (Nair *et al.*, 2007a).

Among the chemical constituents of 'African potato', phytosterols have been suggested to be partly responsible for some of the observed therapeutic and pharmacological properties of the corm's extracts. Mohamed and Ojewole (2003) attributed the hypoglycaemic effect of 'African potato' extracts observed in streptozotocin-induced diabetic rats to phytosterols and sterolins in the extracts of 'African potato'. Phytosterols are known to stabilize plant cell membranes (Nair and Kanfer, 2006b), and are also known to have many therapeutic benefits, including enhancement of immune system in immunocompromised individuals (Bouic *et al.*, 2001; Van Wyk *et al.*, 2002; Nair and Kanfer, 2006b). The antiprostatic adenoma activity attributed to extracts of 'African potato', has also been ascribed to phytosterol glycosides, mainly β-sitosterol glycosides (Hostetmann *et al.*, 2000). These claims, however, remain speculative in view of the fact that daily intake of the same amounts of phytosterols and their glycosides from other plant sources have not produced the same magnitude of therapeutic effects (Hostetmann *et al.*, 2000).

TOXICITY

A recent laboratory report has indicated that chronic infusion of 'African potato' extracts may cause a decrease in glomerular filtration rate, and can elevate plasma creatinine concentrations in rats, suggesting an impairment of kidney function (Musabayane *et al.*, 2005). No

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further reports are available in the biomedical literature to corroborate or dispute this observation. Studies based on experimental animal models have also shown that aqueous extracts of 'African potato' may cause bradycardia and brief hypotension (Ojewole *et al.*, 2006) in guinea-pigs and rats *in vitro* and *in vivo*, respectively; while rooperol has been reported to increase myocardial contractility *in vivo* in baboons, possibly due to its catechol structure (Coetzee *et al.*, 1996). It has been suggested, however, that these cardiovascular effects of 'African potato' extracts may be clinically benign (Albrecht *et al.*, 1995a). The case report of a patient with a known history of ischaemic heart disease who presented with ventricular tachycardia after chronic ingestion of aqueous extract of 'African potato' may be a strong evidence for cardio-toxicity associated with cardio-active chemical compounds present in 'African potato' extracts (Ker, 2005). In South Africa, the national Department of Health (DoH) recently prematurely terminated a clinical study on 'African potato' extracts in HIV-positive patients due to a controversial report of 'bone marrow suppression' in some of the patients (Mills *et al.*, 2005a). At present, it is difficult to clarify these claims, given the charged atmosphere of HIV/AIDS politics in South Africa.

'AFRICAN POTATO' EXTRACTS–DRUG INTERACTIONS

Potential drug interactions between extracts of 'African potato' and antiretroviral drugs have been reported (Mills *et al.*, 2005b). 'African potato' extracts have been reported to inhibit CYP3A4 isoform of cytochrome P_{450} and drug transporter protein (P-glycoprotein). Furthermore, 'African potato' extracts have been claimed to activate drug nuclear receptor pregnane X (PXR) which modulates expressions of both CYP3A4 and P-glycoprotein (Mills *et al.*, 2005b) – see Fig. 1. Many antiretroviral drugs are substrates of CYP3A4, and some herbal preparations are known to alter blood levels of these drugs through their effects on CYP3A4 and P-glycoprotein (Mills *et al.*, 2005c). 'African potato' extracts, therefore, could potentially interact with HIV drug-metabolizing enzymes (Mills *et al.*, 2005a). A recent study (Nair *et al.*, 2007a) which compared various extracts and commercial formulations of 'African potato' extracts interestingly showed that only stigmasterol and rooperol had inhibitory effects on CYP3A4, CYP3A5 and CYP19-mediated drug metabolism. In addition, the study showed that hypoxoside significantly induced P-glycoprotein, compared with ritinovir®. Fairly recent studies (Kuehl *et al.*, 2001; Williams *et al.*, 2002) have also shown that CYP3A5 may represent more than 50% of the total CYP3A isoforms of cytochrome P_{450} in some individuals, and that CYP3A5 has a higher incidence among southern African populations (Williams *et al.*, 2002). CYP19, also known as aromatase, has been implicated in the development of truncal obesity and increased adiposity (due to inhibition of oestrogen synthesis) in patients taking antiretroviral drugs (Toda *et al.*, 1996). No studies have yet been reported about the effect of 'African potato' extracts on organic cation transporters (OCT). It is not unreasonable to speculate, however, that since up-regulation of pregnane X nuclear receptor has been reported, it is likely that 'African potato' extracts would have an effect on cellular drug transport systems (Fig. 1). Taken together, these observations, even though largely *in vitro,* seem to suggest possible *in vivo* interactions between 'African potato' extracts and antiretroviral drugs. Patients taking 'African potato' extracts concurrently with antiretroviral drugs may, therefore, be at risk of developing adverse events which may lead to treatment failure, viral resistance and/or drug toxicity.

CONCLUSION

The therapeutic attributes and pharmaco-chemical profiles of 'African potato' (*H. hemerocallidea* corm) extracts have been reviewed. From available folkloric, anecdotal and laboratory evidence, 'African potato' extracts contain some chemical compounds with anti-inflammatory, antidiabetic, antineoplastic, antiinfective and antioxidant activities. It is highly unlikely that all these potential medicinal properties of 'African potato' extracts could be attributed solely to rooperol and stigmasterol, which are the two main biologically active chemical constituents of the herb so far identified. It is possible that these chemical compounds act in concert together with other compound/s yet to be identified. Certainly, more laboratory and clinical studies are required to clarify this situation. However, the tendency to irrationally commercialize these findings by way of seeking patents, or packaging of the known chemical constituents, may negate genuine efforts to unravel the potential therapeutic mystery of this 'miracle' medicinal plant.

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